Original Article
Clinical characteristics of perivascular space and brain CT perfusion in stroke-free patients with carotid plaque

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Abstract: Aim: This study aimed to investigate characteristics of peri-vascular space (PVS) and CT perfusion and to explore relationship with plaque index (PI) in patients with carotid plaque (CP). Materials and methods: A total of 165 patients were divided into CP and non-CP groups. PI was evaluated. PVS was scored on both sides. Computed tomography perfusion (CTP) was used for determination of perfusion in the region of interest (ROI). Results: Compared with the non-CP group, incidence of whole brain PVS lesions increased significantly in the CP group (P < 0.05). PVS incidence of basal ganglia in the CP group was markedly higher than in the non-CP group (P < 0.05). Further correlation analysis showed that PVS scores of whole brain were positively related with PI (P < 0.01), while PVS scores of basal ganglia were positively associated with PI (P < 0.05). Compared to the non-CP group, blood flow in the whole brain, centrum ovale, and basal ganglia was reduced significantly (P < 0.05). Correlation analysis showed that PI was negatively related to blood flow in the whole brain, centrum ovale, and basal ganglia (P < 0.05). In the basal ganglia, blood flow was negatively related to PVS scores (P < 0.05). Blood flow in the whole brain and centrum ovale was negatively related to PVS scores (P < 0.05). Conclusion: Patients with CP are more susceptible to PVS and the severity of PVS of basal ganglia increases with deterioration of carotid atherosclerosis. There exists a correlation between occurrence and severity of PVS and reduction in focal brain blood flow.

Keywords: Peri-vascular space, brain blood flow, carotid artery, atherosclerosis, plaque index

Introduction

Perivascular space (PVS), also known as Virchow-Robin space (V-R space), refers to the fluid-filled space that follows the typical course of a vessel as it goes through grey or white matter [1]. PVS is characterized by low signals on T1-weighted image (T1WI) and fluid-attenuated inversion-recovery (FLAIR) and high signals on T2-weighted image (T2WI). It appears to be round or oval on the layer vertical to the direction of vessel penetrating and is line-like or tube like (diameter: < 3 mm) on the layer parallel to the direction of vessel penetrating [1]. Previous studies have focused on anatomical and pathological features of PVS. With a wide range of application of MRIs, clinicians have been able to identify PVS visually. Incidence of PVS has increased in the general population, but its etiology and clinical significance remain poorly understood. More studies are necessary to elucidate these issues.

The etiology of PVS is unclear. There is evidence showing that occurrence of PVS is related to brain atrophy [2], immune and inflammation [3], blood brain barrier leakage [4], microvascular embolism [5], age, and hypertension [6]. Recent studies have indicated that the pathogenesis of PVS is closely associated with cerebrovascular lesions, while a certain biological relationship between PVS and cerebral atherosclerosis has been revealed in several studies [7]. However, little is known about the relationship between PVS and carotid atherosclerosis. In the Northern Manhattan Study, Gutierrez et al. found the non-stenotic carotid plaque was a predictor of PVS dilation [8]. In the study of Swieten et al., PVS was not completely related to artherosclerosis in the 9 brain specimens found to be morphologically expanded in the perivascular space [9]. More clinical studies are needed to explore the relationship between carotid plaque and PVS.
Carotid plaque, identified by carotid ultrasonography, is direct evidence of cerebral arteriosclerosis. Carotid ultrasonography has several advantages over other techniques (non-invasiveness, convenience, and intuition). There is evidence showing that the number of PVS at the side of severe carotid stenosis is significantly larger than that on the opposite side [10]. Severe carotid stenosis may alter the hemodynamics, leading to low blood perfusion at the distal end. This study indicates that low blood perfusion to cerebral arteriosclerosis may be an important cause of PVS. However, no studies have examined the relationship between PVS and brain blood perfusion.

Evaluation of whole cerebral arteriosclerosis through carotid intima-media thickness and plaque conditions, detected by carotid ultrasonography, has been a clinical challenge. In some studies, plaque scoring has been employed, in which the sum of thickness of each plaque is used and the score of carotid intima-media thickening is neglected. Thus, this is not suitable for the evaluation and prediction of whole cerebral arteriosclerosis. In this study, plaque index (PI) [11, 12] was determined based on the location, size, and number of plaques, as well as the severity of stenosis. PI is relatively reliable for the evaluation of carotid arteriosclerosis severity and especially sensitive to mild to moderate carotid diseases [12]. PI can be used to not only evaluate the severity of arteriosclerosis [13], but also reflect the influence of plaque on brain blood flow [14].

In this study, carotid ultrasonography was performed to determine carotid intima-media thickness. PI was calculated and the intracranial PVS was evaluated. Focal brain blood flow was assessed in patients without strokes, aiming to explore the relationship among carotid plaques, PVS, and brain blood perfusion.

Materials and methods

General characteristics

A total of 165 patients, without history of strokes, were recruited from the Department of Neurology of Tongji Hospital, from January 2016 to January 2018. All enrolled patients provided written informed consent and were divided into the carotid plaque (CP) group (n = 119) and non-CP group (n = 46), according to the results of carotid ultrasonography. Demographics and risk factors of vascular diseases (such as hypertension, diabetes, hyperlipidemia, smoking, drinking, and homocysteine) were recorded. Data collection was consistent with standard procedures. Carotid ultrasonography, cranial MRIs, and CT perfusion imaging (CTP) were performed. Incidence of PVS was determined for each group.

Inclusion criteria: 1) Informed consent was obtained from patients and their relatives; and 2) There were complete medical history, blood examinations, ultrasonography, and imaging examinations. Exclusion criteria: 1) Patients had a history of or new non-lacunar ischemic strokes or cerebral hemorrhage; 2) There were severe diseases of other systems (such as heart, lungs, liver, or kidneys); 3) There was a history of brain tumors or brain trauma; 4) Patients received implantation of metal devices (such as stents or pacemakers) before admission; 5) Medical records were incomplete; and 6) Patients or their relatives refused to cooperate or were difficult to follow-up.

Methods

Examination of carotid plaque: SonositeX-PORTeColor Doppler ultrasound diagnostic apparatus (USA) was used for carotid ultrasonography (frequency of probe: 5-10 MHz). Patients were asked to lie on a supine position, with heads back, fully exposing the lateral neck. The common carotid artery (CCA; 1.0 cm to the carotid bifurcation), carotid bifurcation (BIF), and origin of internal carotid artery (ICA) (1.0 cm upper to the carotid bifurcation) were examined along the long axis (Figure 1A). Diameter, intima-media thickness (IMT), the location, number and size of plaques, and severity of stenosis were determined and recorded. Carotid plaque was defined as the carotid IMT of ≥ 1.2 mm.

Calculation of PI: According to the Suttontyrell and Alcorn’s method (Suttontyrell, et al., 1993) [12], the IMT of CCA, BIF, and ICA of < 1.2 mm was graded as 0. One small plaque (1.2-2.0 mm or < 30% of vessel diameter) was graded as 1. One medium plaque (2.1-4.0 mm or narrowed 30-50% of vessel diameter or multiple small plaques) was graded as 2. One large plaque (≥ 4.1 mm, or narrowed > 50% of vessel diameter, or multiple plaques with at least one
medium plaque) was graded as 3. If a plaque extended to 2 or 3 segments, the vessel with the thickest intima-media was examined. Connected plaque with protrusions to the lumen were regarded as multiple plaques. The sum of PIs of unilateral CCA, BIF, and ICA was calculated as the unilateral PI, while the sum of PIs of both sides was calculated as the PI of a patient (Figure 1B-E).

MRI: Siemens Verio 3.0T superconducting nuclear magnetic resonance apparatus (Germany) was used for routine cranial MRIs with the following parameters: T1WI: TR, 1530 ms, TE, 9 ms; T2WI: TR, 4210 ms, TE, 96 ms; FLAIR: TR, 5000 ms, TE, 94 ms, TI, 1800 ms; Slice thickness: 5 mm; interval: 1 mm; FOV: 230 mm × 230 mm.

PVS scoring: Assessment was done at the layers of centrum ovale and basal ganglia. PVS was defined as the presence of spinal cord fluid signals on all MRI sequences with diameters < 3 mm [1], with exclusion of lacunar infarcts and lacunas. The Doubal and Macullich method [15] was used for assessment of PVS, carried out by an experienced neurologist on T1, T2, and FLAIR images. PVS was scored on T2 images as follows: 0, no PVS; 1, ≤ 10 PVS; 2, 11-20 PVS; 3, 21-40 PVS; 4, ≥ 40 PVS. The number of PVS was determined on both sides and total PVS scores were calculated (0-16), with PVS scores of the centrum ovale of 0-8 and PVS scores of basal ganglia of 0-8 (Figure 2).

CT scan: Toshiba Aquilion ONE 320 volume CT was performed for whole brain perfusion determination with coverage of 140 mm, volume scanning, slice thickness of 0.5 mm, matrix of 512 × 512, tube voltage of 100 kV, and tube current of 150 mA. First, 50 mL of contrast reagent (350 mgI/mL Lohexol) was injected at a rate of 5 mL/s into the anterior elbow vein. The first scanning was done 7 seconds later. Scanning was then done with an interval of 2 seconds from 12 seconds. From 40 seconds, the scanning was done with an interval of 5 seconds. The total scan duration was 60 seconds and the single rotation time was 0.5 s. A total of 19 volume data were obtained.

Image processing and acquisition: A total of 19 volume data were input into the workstation. The Perfusion Mismatch Analyzer (Advanced Medical Science Center, Iwate Medical) was used for determination of cerebral blood flow (CBF). Perfusion images were analyzed with the deconvolution method with the matrix of 512 ×
512, slice thickness of 0.1 mm, and default values of other PMA data. For quantitative analysis, perfusion images after PMA reconstruction were input into Mango software (http://rii.uthscsa.edu/mango/) and the region of interest (ROI) was delineated. The CBF was determined at the layers of centrum ovale and basal ganglia (Figure 2C, 2D).

**Statistical analysis**

Statistical analysis was conducted with SPSS version 21.0. Data are expressed as mean ± standard deviation (X ± s) and comparisons were done with t-test. Qualitative data were compared with Chi-squared test. A value of P < 0.05 indicates statistical significance. Correlation analysis was performed with Spearman's correlation analysis, with a value of two-sided P can reliably assess the degree of atherosclerosis through parameters, such as plaque thickness, stenosis rate, and location, the PI of the common carotid artery, carotid bifurcation, and internal carotid artery was calculated. The PI of the posterior wall of a carotid bifurcation can be calculated at 0-3 (Figure 1), which represents the degree of atherosclerosis in this segment. Further analysis showed that total PVS scores were positively correlated with PI (r = 0.244, P < 0.01). PVS scores of the centrum ovale had no relationship with PI (P > 0.05), but PVS scores of basal ganglia were closely related to PI (r = 0.243, P < 0.01) (Figure 3B-D).

**CBF in both groups**

Compared to non-CP group, the CBF of whole brain, centrum ovale, and basal ganglia was
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Correlation between PVS scores and CBF

Regional cerebral blood flow decreased in patients with PVS (Figure 2C, 2D) and was associated with PVS scores. Results showed that PVS scores of basal ganglia were negatively related to the CBF of basal ganglia ($r = -0.161, P < 0.05$). Total PVS scores were negatively related to the CBF of whole brain ($r = -0.246, P < 0.01$), while PVS scores of the centrum ovale were negatively related to the CBF of centrum ovale ($r = -0.185, P < 0.05$) (Figure 5A-C).

Discussion

Increased incidence of intracranial PVS in patients with carotid plaque may be related to more severe cerebral arteriosclerosis in these patients. Some studies have confirmed that carotid arteriosclerosis is a part of systemic arteriosclerosis, reflecting the severity of whole brain arteries [16-18]. There is evidence showing that carotid atherosclerotic plaque and intima-media thickness increase in patients with intracranial microvascular or macrovascular lesions [19]. Gutierrez et al. conducted the Northern Manhattan study, in which 706 patients without strokes were recruited [8]. Their results showed that PVS was closely related to carotid plaque. However, Xiao et al. found that severity of PVS was negatively related to risks for intracranial arterial sclerosis [20]. Present results showed that incidence of PVS increased significantly in patients with carotid plaque. In the present study, PI was employed to evaluate carotid arteriosclerosis. It was shown as a favorable indicator reflecting the severity of whole brain arteriosclerosis [13, 18, 21]. In this study, the relationship between PI and PVS was evaluated, with results showing a positive correlation between them. This indicates that PI, as an indicator of carotid arteriosclerosis, can be used to predict intracranial PVS in clinical practice. Of note, the sample size was small in

Figure 3. Incidence of PVS of whole brain, centrum ovale, and basal ganglia, as well as the correlation between PVS scores and PI. A: Incidence of PVS at the whole brain, centrum ovale, and basal ganglia; B: Correlation between PI and PVS of whole brain; C: Correlation between PI and PVS of centrum ovale; D: Correlation between PI and PVS of basal ganglia.
this study. More clinical studies with larger sample sizes are necessary to confirm present findings.

Interestingly, current results showed that severity of carotid arteriosclerosis was closely related to PVS scores of basal ganglia but had no relationship with PVS scores of the centrum ovale. Brutto et al. [7] employed Carotid siphonic calcification for the evaluation of intracranial arterial sclerosis, finding that intracranial carotid arteriosclerosis was related to the PVS of basal ganglia. However, in their study, the authors speculated that the PVS of the centrum ovale was attributed to other factors. Thus, they did not compare PVS scores of the centrum ovale between groups [22]. Song et al. [23] found that incidence of aortic plaque in
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acute stroke patients with overall PVS dilation at centrum ovale and basal ganglia was 3 times higher than that in control group. However, they did not evaluate the relationship of PVS of centrum ovale and basal ganglia with plaque. In the present study, the relationship of PI with PVS scores of the centrum ovale and basal ganglia was further evaluated. Results demonstrated that intracranial and extracranial arteriosclerosis was related to the PVS of basal ganglia, but arteriosclerosis was not associated with the PVS of centrum ovale. Elevated incidence of PVS at basal ganglia may be ascribed to the susceptibility of basal ganglia to arteriosclerosis. One possible reason can be that the blood supply to the basal ganglia is based on the branches of gingival arteries vertically originating from the middle cerebral artery. These branches are susceptible to arteriosclerotic lesions and subsequent arterial wall injuries and PVS dilation. Available studies have confirmed that the arterioles in the basal ganglia are more susceptible to arteriole arteriosclerosis and hyalinosis [24]. However, the pathogenesis of PVS at the centrum ovale might be related to non-vascular factors, such as amyloid deposition and mild traumatic brain injuries [5, 6, 25].

Currently, there is controversy concerning the relationship between carotid plaque and brain perfusion. In some studies with spin labeling MRIs, results showed that the CBF of carotid plaque patients reduced at the frontal lobe, parietal lobe, temporal lobe, and basal ganglia [26]. In one study, single photon emission computed tomography (SPECT) was employed to analyze the CBF at different lobes of the brain [27]. Results showed that CBF reduced in the frontal, parietal, and temporal lobes. In some studies, CT perfusion imaging was employed to evaluate the CBF in regions supplied by intracranial major arteries (anterior, middle, and posterior cerebral arteries), watershed region, and basal ganglia [28]. Results showed that the CBF in the region supplied by posterior cerebral artery and basal ganglia was not decreased significantly, but reduced CBF was also found in other regions. This discrepancy in available studies might be related to differences in methodology. SPECT has poor performance in the early detection of chronic cerebral hypoperfusion and poor sensitivity to the white matter ischemia. Data of CBF determined by spin labeling MRIs are unstable and semi-quantification is difficult. CT perfusion imaging, however, is rapid, simple to operate, and tolerant to patients. In this study, CT perfusion imaging was employed. Results showed that whole brain CBF reduced in patients with carotid plaque, consistent with the findings of Jing et al. [29].

The study of Sahin et al. indicates that cerebral arteriosclerosis causing hypoperfusion in the corresponding brain region may be a cause of PVS [10], but they did not determine the brain CBF in patients with carotid arteriosclerotic plaques. Present results showed that incidence of PVS at basal ganglia increased in patients with carotid plaque. Furthermore, CT perfusion imaging was employed to determine the CBF of the basal ganglia. Results indicate that the CBF of basal ganglia in patients with carotid plaque was lower than that in controls, consistent with the findings of previous studies [29]. In addition, results also indicate that the CBF of basal ganglia was negatively related to PVS scores of basal ganglia. To the best of our knowledge, the present study, for the first time, reported the relationship between CBF of basal ganglia and PVS in patients with carotid arteriosclerosis. Results suggest higher carotid PIs indicate lower brain perfusion and higher likelihood of PVS of arteriosclerosis. It has been confirmed that the basal ganglia are supplied by the terminal branches of the striate artery. There is no anastomotic branch and the vascular density is also lower. Thus, the basal ganglia is susceptible to arteriosclerosis, which may cause focal ischemia and lower perfusion [30], leading to insufficient energy metabolism in vessels and surrounding cells, vascular leakage, vascular atrophy, and thinning and presence of microspace. Similarly, present results showed that total PVS scores were negatively related to blood flow in the whole brain, while PVS scores of the centrum ovale were negatively related to blood flow in the centrum ovale.

Studies have confirmed that low perfusion can affect PVS via different ways: (1) Low perfusion may increase MMP-2 to degrade tight junction protein [31], which then opens the tight junctions, disrupts the blood brain barrier, and increases permeability; (2) Nitric oxide synthase is acetylated [32] and the balance of physiological energy regulation is interrupted;
and (3) Glial cells are activated and aquaporin 4 (AQP4) is re-distributed [33]: intravascular AQP4 expression reduces, but AQP4 expression increases significantly in the extravascular parenchyma. More studies with advanced techniques are needed to explore the exact causes of PVS secondary to low brain perfusion.

To date, the pathogenesis of PVS dilation remains unclear. This was preliminarily explored in the current study. In the present study, axial images used as the sole planes for assessment of PVS might have underestimated the volume of vertical spaces larger than 3 mm in diameter. Thus, PVS should be evaluated at sagittal and/or coronal planes in future studies. In addition, it is necessary to investigate the sclerosis of vessels with different sizes in the basal ganglia of patients with carotid plaque, which may make findings more convincing. This was a cross-sectional study. More follow-up studies are needed to investigate the causal relationship between occurrence and development of carotid atherosclerosis and PVS.

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Disclosure of conflict of interest

None.

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References


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